Amendments to the Figures

The attached sheets of replacement formal drawings include changes to Figures 1-25.

Replacement Sheet 1/25, which includes Figure 1, replaces the original Figure 1 page.

Replacement Sheet 2/25, which includes Figure 2, replaces the original Figure 2 page.

Replacement Sheet 3/25, which includes Figure 3, replaces the original Figure 3 page.

Replacement Sheet 4/25, which includes Figure 4, replaces the original Figure 4 page.

Replacement Sheet 5/25, which includes Figure 5, replaces the original Figure 5 page.

Replacement Sheet 6/25, which includes Figure 6, replaces the original Figure 6 page.

Replacement Sheet 7/25, which includes Figure 7, replaces the original Figure 7 page.

Replacement Sheet 8/25, which includes Figure 8, replaces the original Figure 8 page.

Replacement Sheet 9/25, which includes Figure 9, replaces the original Figure 9 page.

Replacement Sheet 10/25, which includes Figure 10, replaces the original Figure 10 page.

Replacement Sheet 11/25, which includes Figure 11, replaces the original Figure 11 page.

Replacement Sheet 12/25, which includes Figure 12, replaces the original Figure 12 page.

Replacement Sheet 13/25, which includes Figure 13, replaces the original Figure 13 page.

Replacement Sheet 14/25, which includes Figure 14, replaces the original Figure 14 page.

Replacement Sheet 15/25, which includes Figure 15, replaces the original Figure 15 page.

Replacement Sheet 16/25, which includes Figure 16, replaces the original Figure 16 page.

Replacement Sheet 17/25, which includes Figure 17, replaces the original Figure 18 page.

Replacement Sheet 18/25, which includes Figure 18, replaces the original Figure 19 page.

Replacement Sheet 19/25, which includes Figure 19, replaces the original Figure 20 page.

Replacement Sheet 20/25, which includes Figure 20, replaces the original Figure 21 page.

Replacement Sheet 21/25, which includes Figure 21, replaces the original Figure 22 page.

Replacement Sheet 22/25, which includes Figure 22, replaces the original Figure 22 page.

Replacement Sheet 23/25, which includes Figure 23, replaces the original Figure 23 page.

Replacement Sheet 24/25, which includes Figure 24, replaces the original Figure 24 page.

Replacement Sheet 25/25, which includes Figure 25, replaces the original Figure 25 page.

REMARKS

The Drawings submitted 19 June 2002 were deemed not acceptable. Replacement drawings as well as Annotated drawings are included.

The amendments to the specification were objected to as being improper. However, the applicants submit that the amendments were proper as filed, as the amendments did show changes.

Claim 16 is objected for containing two periods. Claim 16 has been amended.

Claims 1-19 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Claim 1 has been amended at line 3 and line 4 for technical clarity.

Claim 15 has been amended for technical clarity.

Claim 17 has been amended to be dependent on Claim 16 and correct antecedent basis is established.

Claims 1-4, 8, 14 and 17-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gao et al. in view of Stimpson et al.

Gao et al. utilizes epipolarization microscopy. In this system, Gao et al. labels the sample with colloidal gold, crosslinks the surface, enhances the gold with silver, and shines polarized light down upon it. Epipolarization microscopy utilizes epi-illumination, that is, same side illumination. As shown in Figure 5 of Gao et al., the light that is captured by the CCD camera has two sources. First, "normal light" which is projected from the bottom of the sample (see the Tungsten light at the bottom of Figure 5 and the notation of the solid line under the CCD camera as "normal light for tissue profile" at the top of Figure 5). The second captured light is the light that generated from the Mercury vapor lamp, polarized and is reflected off the Au-Ag

particles (see the "Depolarized light for Au-Ag signal" under the CCD camera at the top of Figure 5). Essentially, Gao's system relies on the use of polarized light and subsequent depolarization if the Au-Ag particles are present to generate an image. Epipolarization microscopy reads as bright spots (e.g. the silver enhanced colloidal gold) in a dark background. This method is also shown in Figure 1 of Gao, which shows that the polarized light (e; wavy line) hits the silver-enhanced gold (d) and reflects rotated-polarized light (f; solid line) back to the detector.

Stimpson teaches assay methods using the detection of scattered light from the surface of an evanescent wave guide. In particular, Stimpson's preferred imaging processing is done by illuminating the entire waveguide at once, and allowing the detection of real time binding.

The Examiner states that it would be obvious to modify Gao with Stimpson in order to detect binding analytes. As a preliminary matter, as the Examiner is aware, a *prima facie* case of obviousness requires a motivation to combine the references, and the initial burden of establishing a *prima facie* case falls to the Examiner ; see M.P.E.P. §2142. In the present case, the Examiner has not presented "a convincing line of evidence" as to why one of skill in the art would combine epipolarization microscopy with light scattering technology. These are two fundamentally different imaging techniques. The Applicants respectfully submit that it is not obvious to combine epipolarization microscopy with Stimpson's light scattering techniques.

Claims 5, 9-13, and 15 are rejected under 35 U.S.C. §103(a) over Gao et al. in view of Stimpson and further in view of De Brabander.

Gao and Stimpson are outlined above. The defects of this combination are not corrected by the addition of De Branbander, and thus the rejection should be withdrawn.

Claims 6-7 and 16 are are rejected under 35 U.S.C. §103(a) over Gao et al. in view of Stimpson and further in view of Oberhardt.

Gao and Stimpson are outlined above. The defects of this combination are not corrected by the addition of Oberhardt, and thus the rejection should be withdrawn.

Conclusion

The claims are now in condition for allowance and an early notification of such is kindly solicited. Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

DORSEY & WHITNEY LLP

Dated: 6/13/05

By: Robin M. Silva

Four Embarcadero Center
Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989
Fax No. (415) 398-3249

Robin M. Silva, Reg. No. 38,304
Filed under 37 C.F.R. § 1.34

Customer No. 32940

Annotated Sheet

1/25

Aggregate vs. Scanning Ellipsometry

Innovation Group

Standard Immunoassay Use

Determination of mass per unit volume (eg. ng/ml) or equivalent (eg. IU)

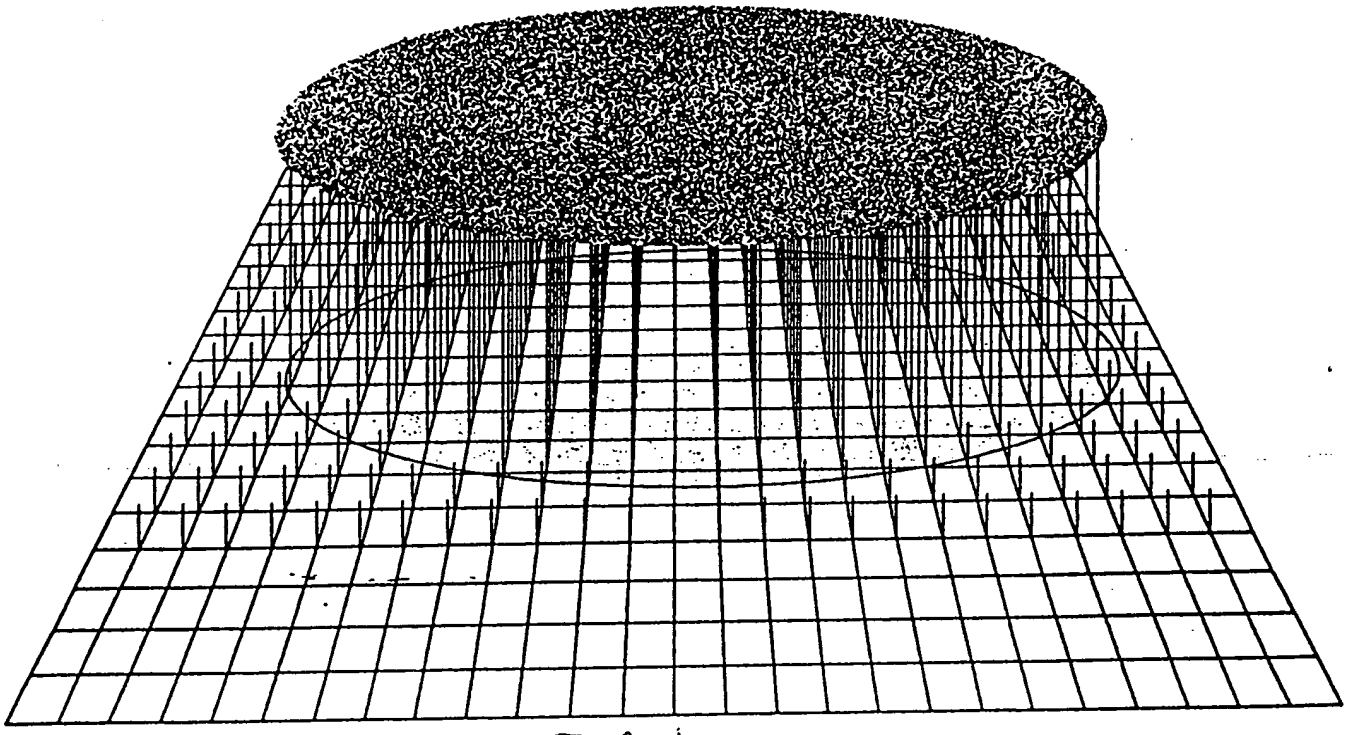

FIG. 1

The effect of the use of a single large beam (in this case approx. 2mm) for reading the surface is the production of a single result representing the mass change effects of all binding events within the spot area.

Figure 1

Annotated Sheet

2/25

Aggregate vs. Scanning Ellipsometry

Innovation Group

Standard Immunoassay Use

Determination of mass per unit volume (eg. ng/ml) or equivalent (eg. IU)

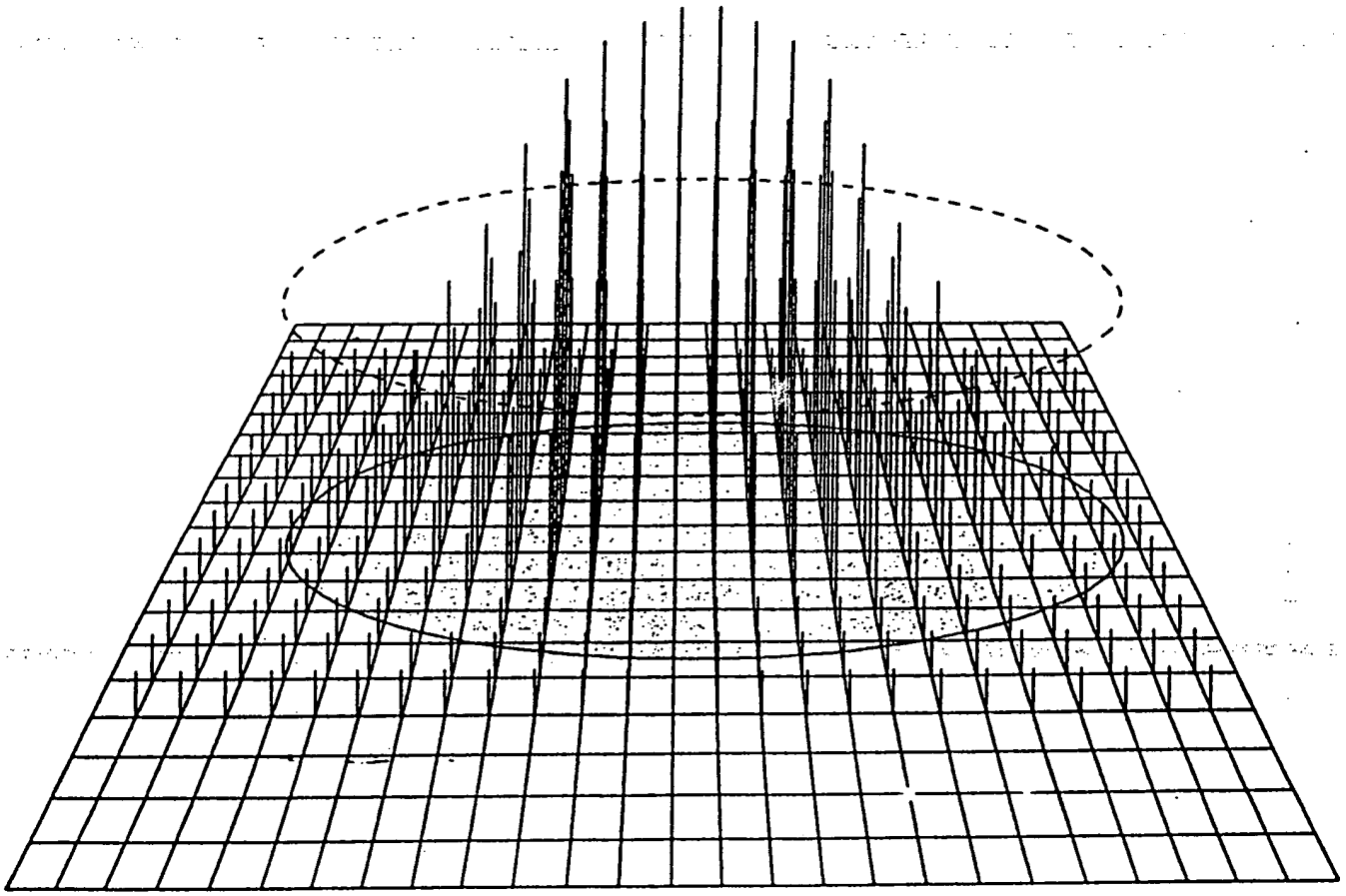

FIG. 2

The idealized model for this method is the optical averaging occuring over the entire read area (in this case represented by an approx. normal distribution of binding events over the spot area).

Figure 2

Aggregate vs. Scanning Ellipsometry

Innovation Group

Standard Immunoassay Use

Determination of mass per unit volume (eg. ng/ml) or equivalent (eg. IU)

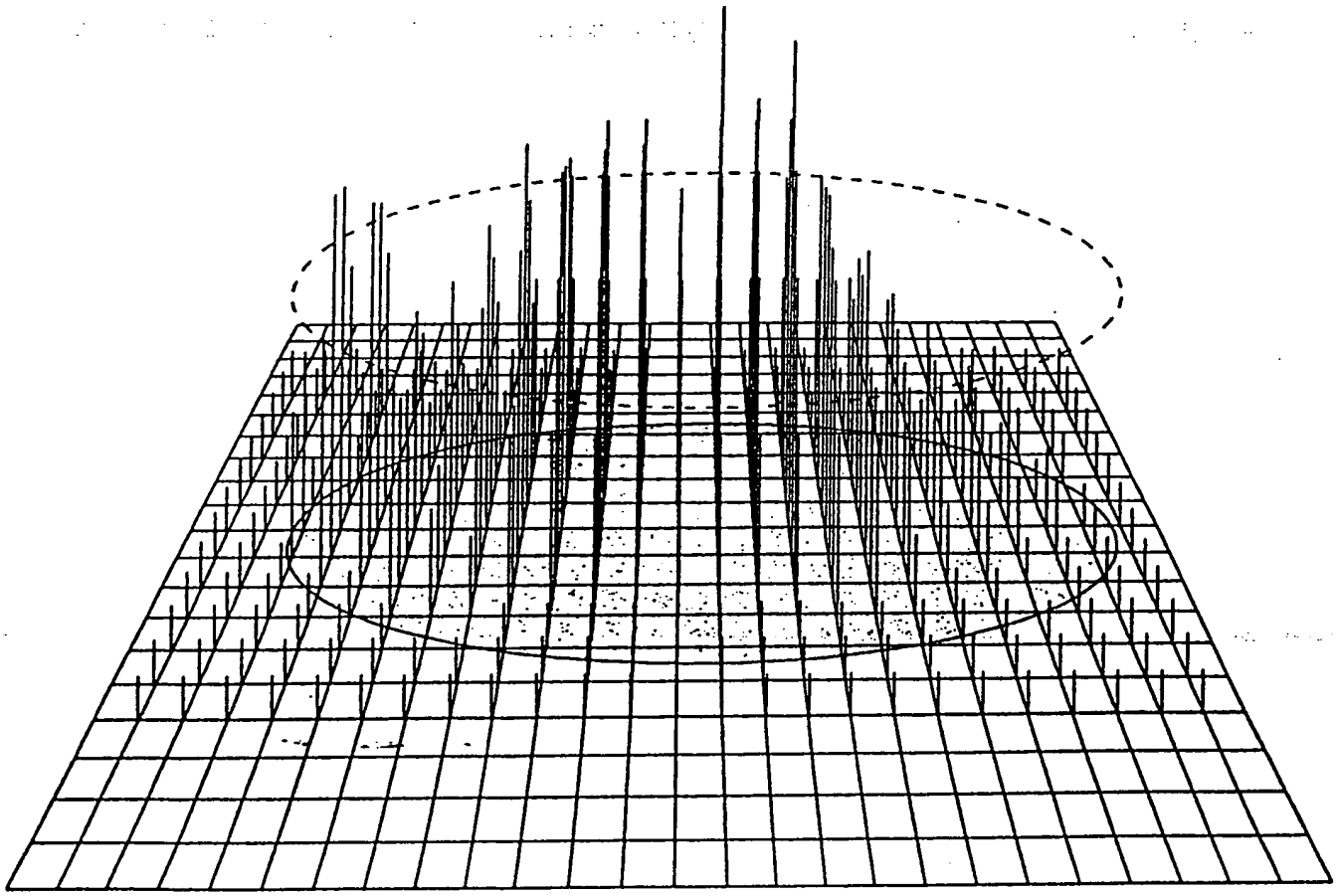

FIG. 3

In virtually all cases the binding distribution over the spot area is actually highly inhomogenious. The advantage of this method is that it inherently integrates all of the binding events within the spot area, without regard to their distribution.

Figure 3

Annotated Sheet

4/25

Aggregate vs. Scanning Ellipsometry

Innovation Group

Standard Immunoassay Use

Determination of mass per unit volume (eg. ng/ml) or equivalent (eg. IU)

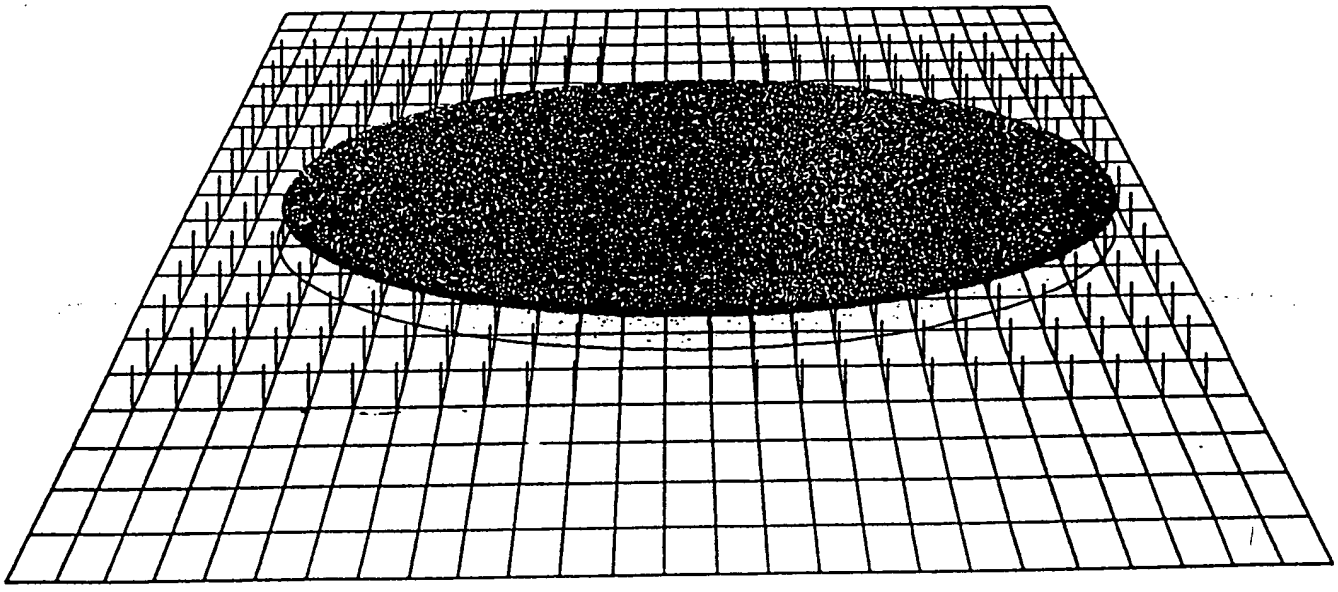

FIG. 4

The disadvantage is that very small or very sparce binding events tend to be statistically reduced to insignificance when averaged over this relatively large spot area.

Figure 4

Annotated Sheet

5/25

Aggregate vs. Scanning Ellipsometry

Innovation Group

New Microbiological Use

Determination of individual binding events or CFUs

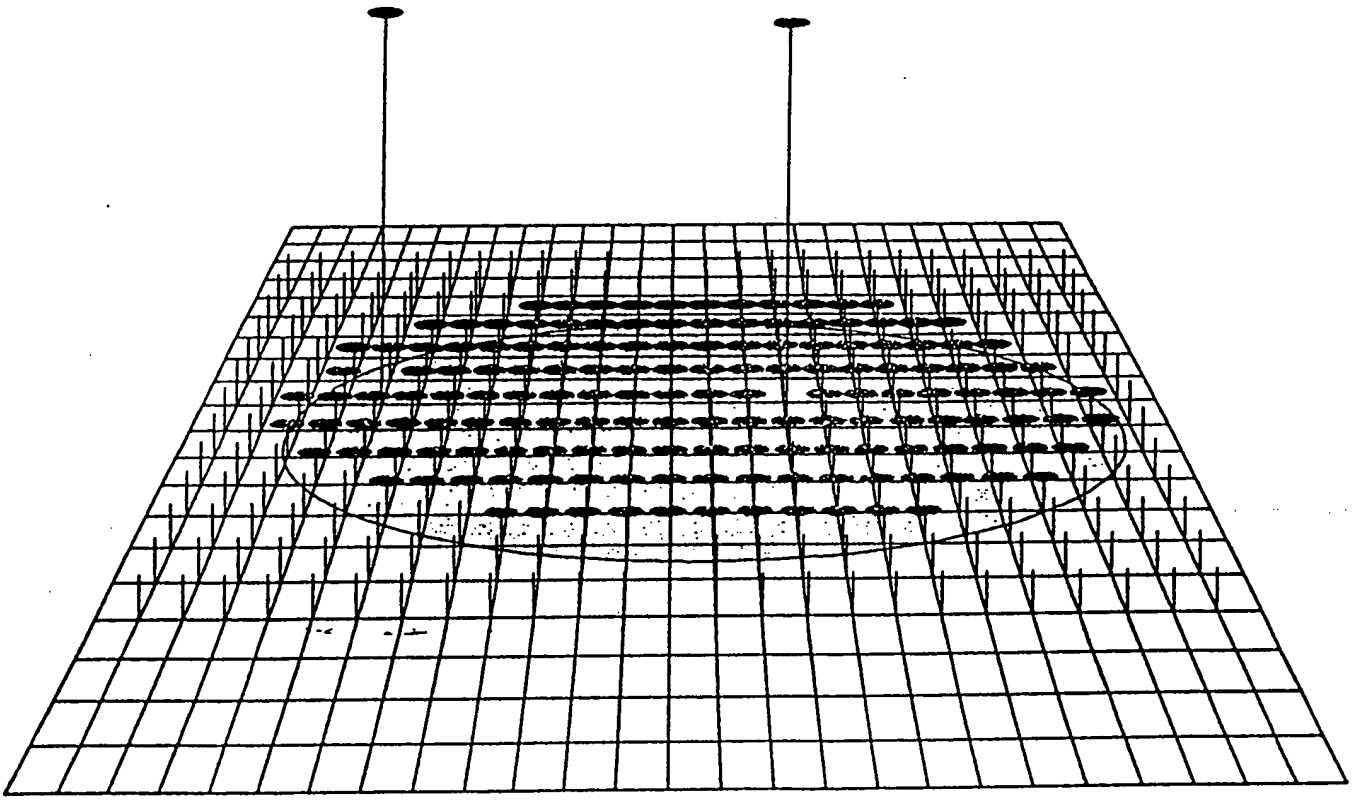

Fig. 5

A scanning ellipsometric method or scatterometric method or both, when used with a very small beam diameter (in this case 20um) can provide a vastly higher relative signal for discreet binding events (that is as averaged over a much smaller spot area).

Figure 5

Annotated Sheet

6/25

Aggregate vs. Scanning Ellipsometry

Innovation Group

New Microbiological Use

Determination of individual binding events or CFUs

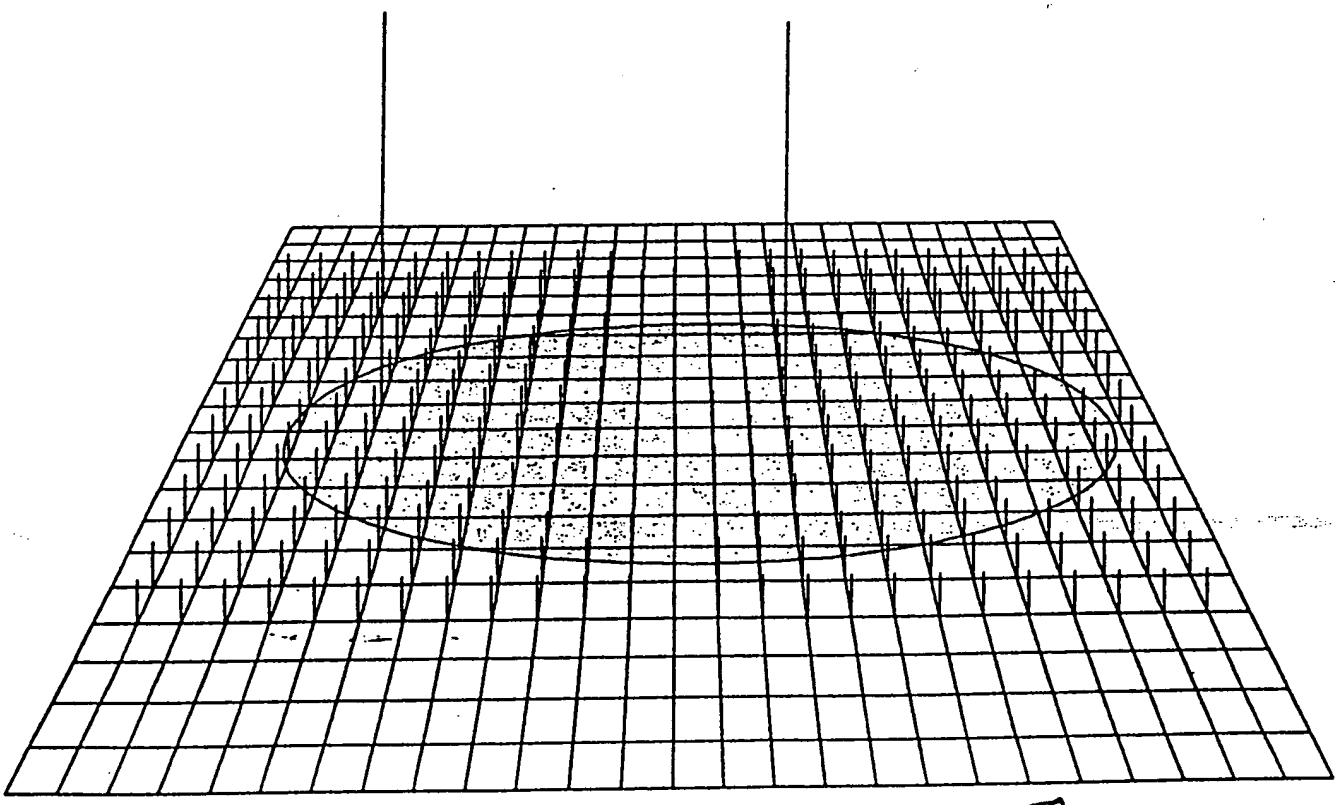

Fig. 6

This approach allows for the surface to be resolved as a type of topology. It is, in fact, because the binding events are not integrated over the surface that this method can be used to approximate individual or discreet binding event identification (depending upon the diameter of the beam used).

Figure 5

Annotated Sheet

7/25

Innovation Group

Aggregate vs. Scanning Ellipsometry

Current OTER Laser Configuration

Determination of aggregate response over the beam spot area

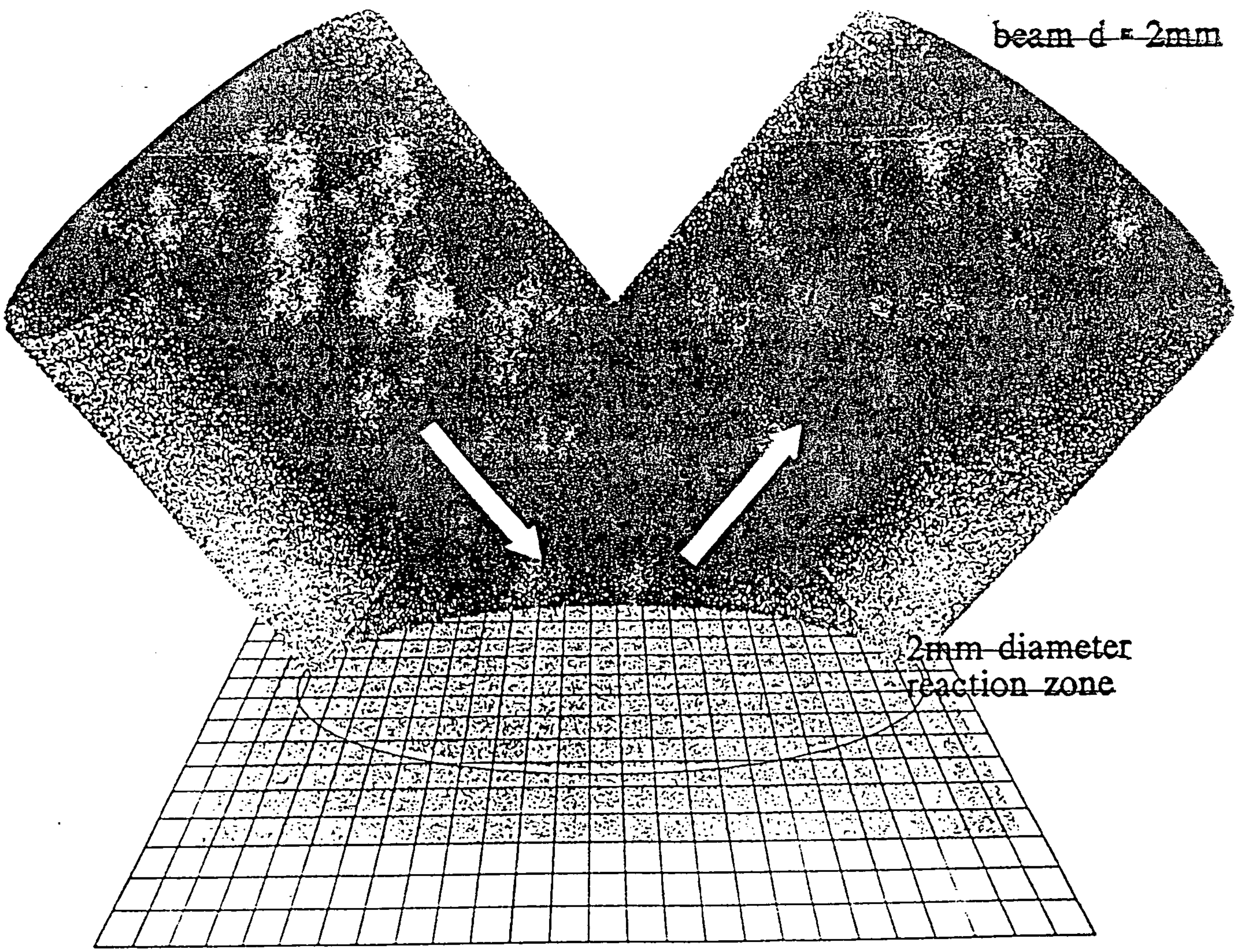

Fig.7

pi•r^2 = SA (in mm.^{2}) = 3.14159 x 1^2 = 3.14159 mm^2

Figure 7

Figure 7 is oriented to landscape view

Annotated Sheet

8/25

Innovation Group

Aggregate vs. Scanning Ellipsometry

Scanning Micro-Laser Configuration
Determination of individual cellular-scale readings

For Example:
beam d = 20um

In the example where the reaction zone is 2mm in diameter, and the scanning beam is 20um in diameter, there can be 100 discreet measurements along the diameter.

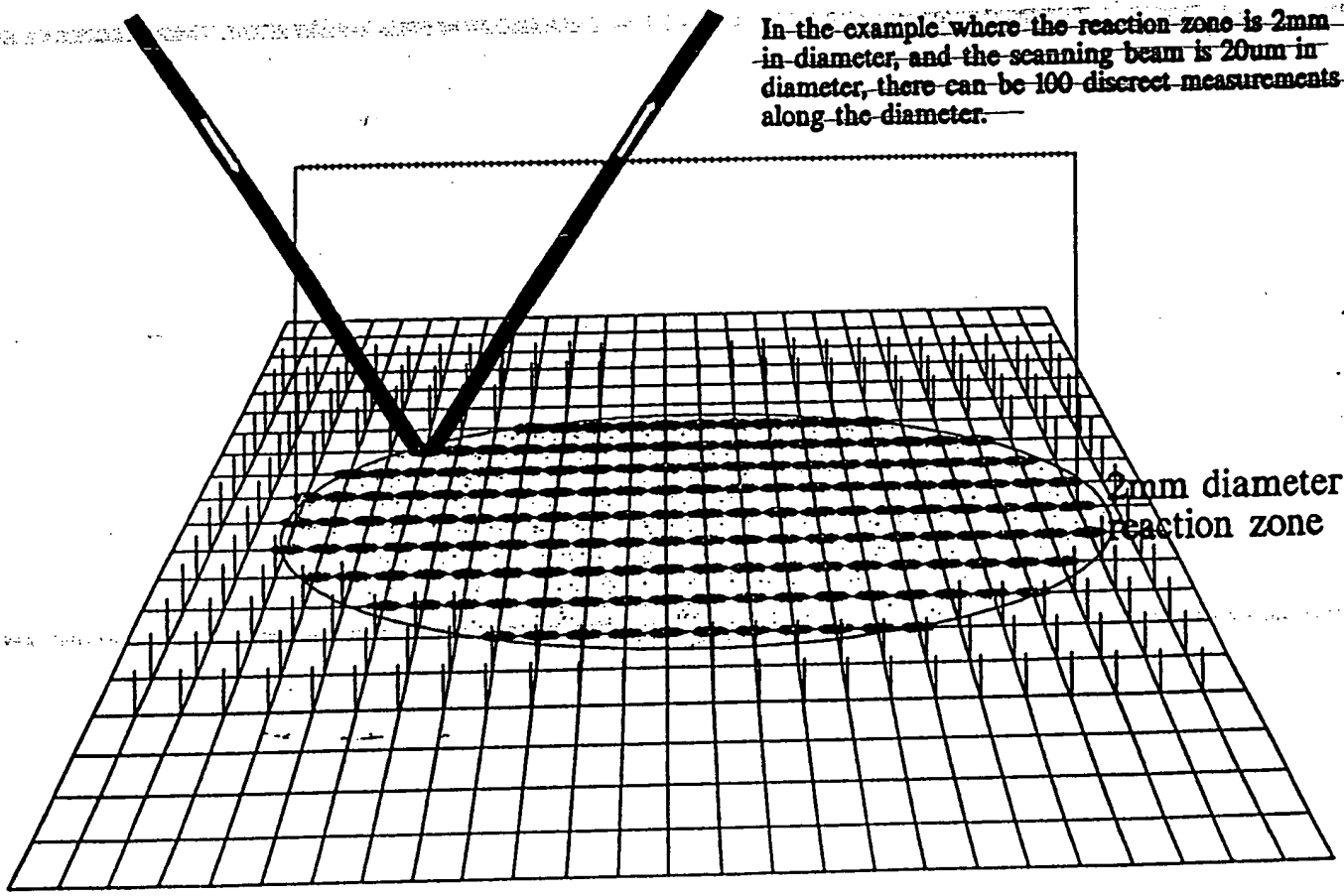

Fig. 8

10,000 A = 1um
1,000um = 1mm
Angstrom Unit = 3.937x10^-9 inch, 1x10^-10 meters, 1x10^-4, microns, 0.1 milli-micron (micro millimeter).
Micron = 3.937x10^-5 inch, 0.039370 mil, 1x10^-6 meter, 0.001 millimeter, 1x10^4 Angstrom units.

$1\ mm^2 = 1{,}000{,}000\ um^2$ Reaction zone SA = $3{,}141{,}590\ um^2$ Scanning beam reads $314.159\ um^2$

Thus a 20um beam can make 10,000 discreet readings within the reaction zone

Figure 8

Annotated Sheet

9/25

Aggregate vs. Scanning Ellipsometry

How Big is Small ?

In the case where a single organism (1 um^3) is to be measured on a 2 mm^2 surface:

314,159,000,000,000 A^2 surface area of spot
78,500,000 A^2 surface area of organism → ratio of 4,000,000 A^2 : 1 A^2

10,000 A (height) / 4,000,000 = .00250 A (height) contribution across the spot

1×10^2 cells / .02ml = 5×10^3 cells / ml → .25 A (height) contribution across the spot
1×10^3 cells / .02ml = 5×10^4 cells / ml → 2.5 A (height) contribution across the spot
1×10^4 cells / .02ml = 5×10^5 cells / ml → 25 A (height) contribution across the spot
1×10^5 cells / .02ml = 5×10^6 cells / ml → 250 A (height) contribution across the spot
1×10^6 cells / .02ml = 5×10^7 cells / ml → 2500 A (height) contribution across the spot

probable unamplified detectability limit

With an amplification system that provided 2X mass, the system needs 2.5×10^6 cells / ml
With an amplification system that provided 5X mass, the system needs 1×10^6 cells / ml
With an amplification system that provided 10X mass, the system needs 5×10^5 cells / ml

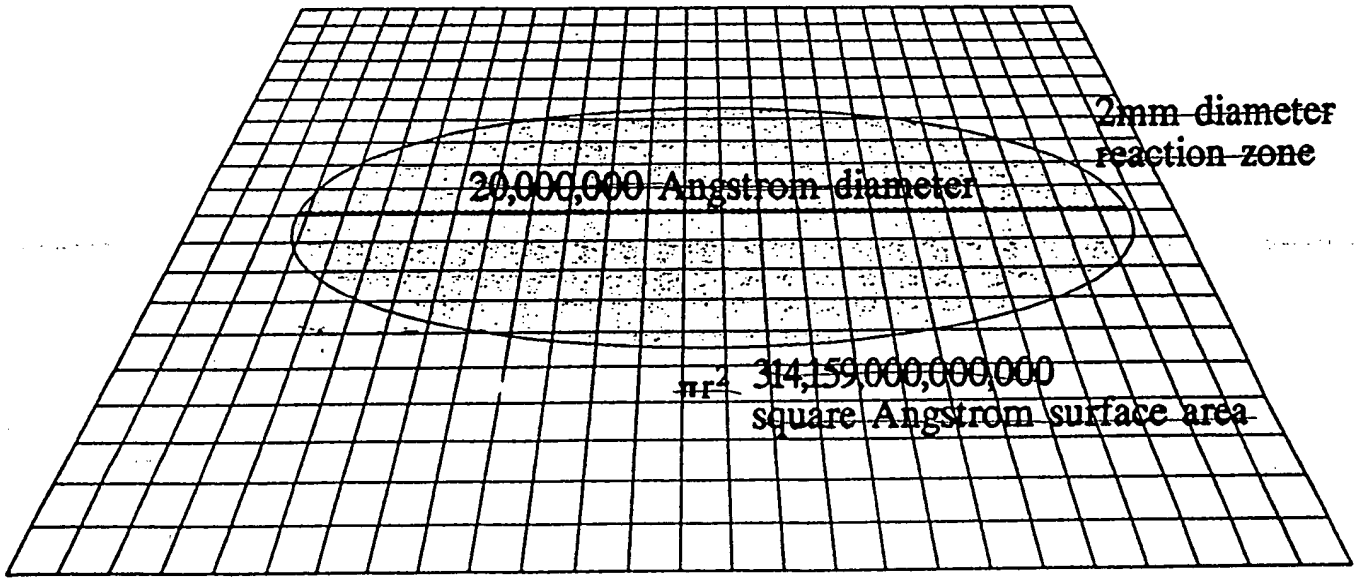

Fig. 9

10,000 A = 1um
1,000um = 1mm
Angstrom Unit = 3.937x10^-9 inch, 1x10^-10 meters, 1x10^-4, microns, 0.1 milli-micron (micro-millimeter)
Micron = 3.937x10^-5 inch, 0.039370 mil, 1x10^-6 meter, 0.001 millimeter, 1x10^4 Angstrom units

Figure 9

Annotated Sheet

1925

Innovation Group

Scanning vs. Array Ellipsometry

An alternative to the small beam "Scanning" approach is the use of a CCD or diode array to read and "parce" the larger laser beam into smaller discreet signals.

Determination of small spot response within the large beam spot area

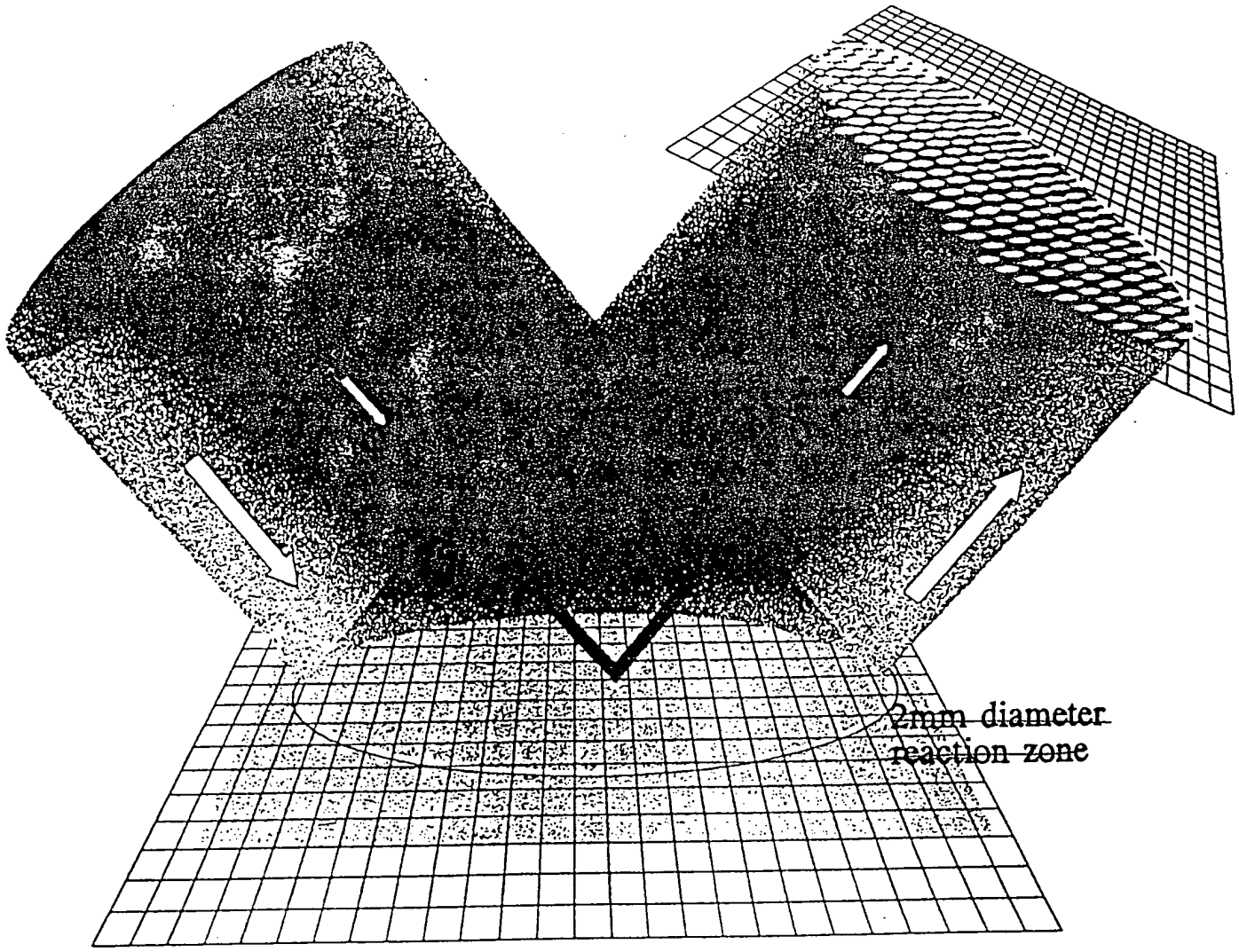

Fig. 10

This effectively creates a "virtual" beam (defined by the path that the light intersecting the array at a specific dection point has taken).

The aggregate signal for all virtual beams equals the large beam signal, but each virtual beam references only a limited surface area. The virtual beam approach may be subject to greater error than the small beam approach, due in part to the potential for signal mixing across the array, however it allows for a major increase in sensitivity over the large beam approach.

Figure 10

Figure 10 is oriented in landscape view

Annotated Sheet

11/25

Various Optical Signal Formats

Innovation Group

The specific optical signal can be selected so as to provide the appropriate level of information, based upon the nature or the material to be detected, and the resolution desired.

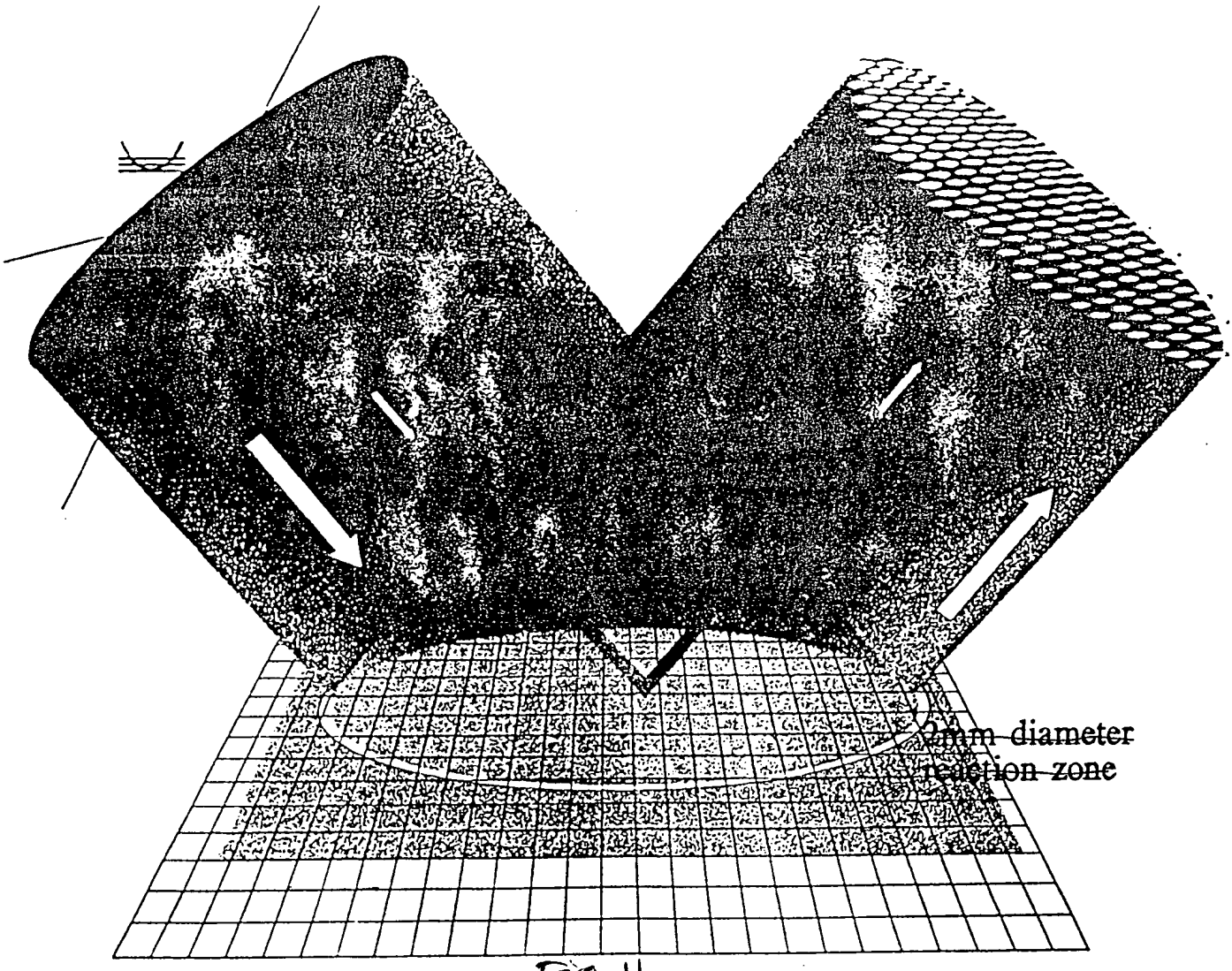

Fig. 11

A variety of optical signals may be used within this system.

The examples provided in this discussion use ellipsometry as the example optical method. However it is expected that a variety of optical methods will be substantially improved by adopting the general approach described here. In particular we have demonstrated that scattering methods will form the basis of one class of instruments that is distinct from ellipsometry. Other effects such as absorption, refractive index change, chiral effects, and diffraction may be used within an essentially similar ical configuration, and may provide particular and significant benefits.

Figure 11

Annotated Sheet

12/25

Examples of Optical Signal Formats

~~Innovation Group~~

Principle	Label Type	Instrument	DDx Status
Scatter	polymer beads/particles silica beads/particles magnetic beads/particles metal beads/particles metal coated beads/particles	scatterometry	demonstrated
Optical absorption	colloidal gold magnetic beads	reflectometry photometry	scheduled
Change in polarization state	polymer beads silica beads	ellipsometry (with compensator) polarimetry (wout compensator)	scheduled
Change in refractive index	high refractive index or optically active materials	ellipsometry (with compensator) polarimetry (wout compensator)	scheduled
Chiral effects	azio dyes chiral compounds		envisioned
Diffraction effects	patterned surface	interferometry	envisioned
Spectroscopic effects	wavelength selective materials	spectrometer	envisioned

~~Signal reception techniques might include:~~

~~single diode detector - e.g. scanning (small beam method)~~
~~diode array detector - e.g. array (virtual beam method)~~
~~CCD detector - e.g. array (virtual beam method)~~

Figure 12

Annotated Sheet

13/25

Potential for Optical Enhancement

Innovation Group

For either the Scanning (small beam) or the Array (virtual beam) approach, a substantial improvement in signal delectability may be possible by using unique characteristics of optically based mass detection systems.

Properties of the mass enhancement label may alter the optical signal due to a number of physical characteristics, including:

- refractive index
- scatter
- chiral effect
- general adsorption
- wavelength specific adsorption
- diffraction

} Aren't it be absorbance = What's the difference between these two?

effectively creating an improved ability to discriminate the signal generated by the binding of the label to the complex from that created by surface background or in the absence of specific binding events. This may operate through the creation of an enhanced or attenuated "apparent" signal over that which would be created by "normal" materials.

Scale of normal vs. optically active elements @ 2X effect

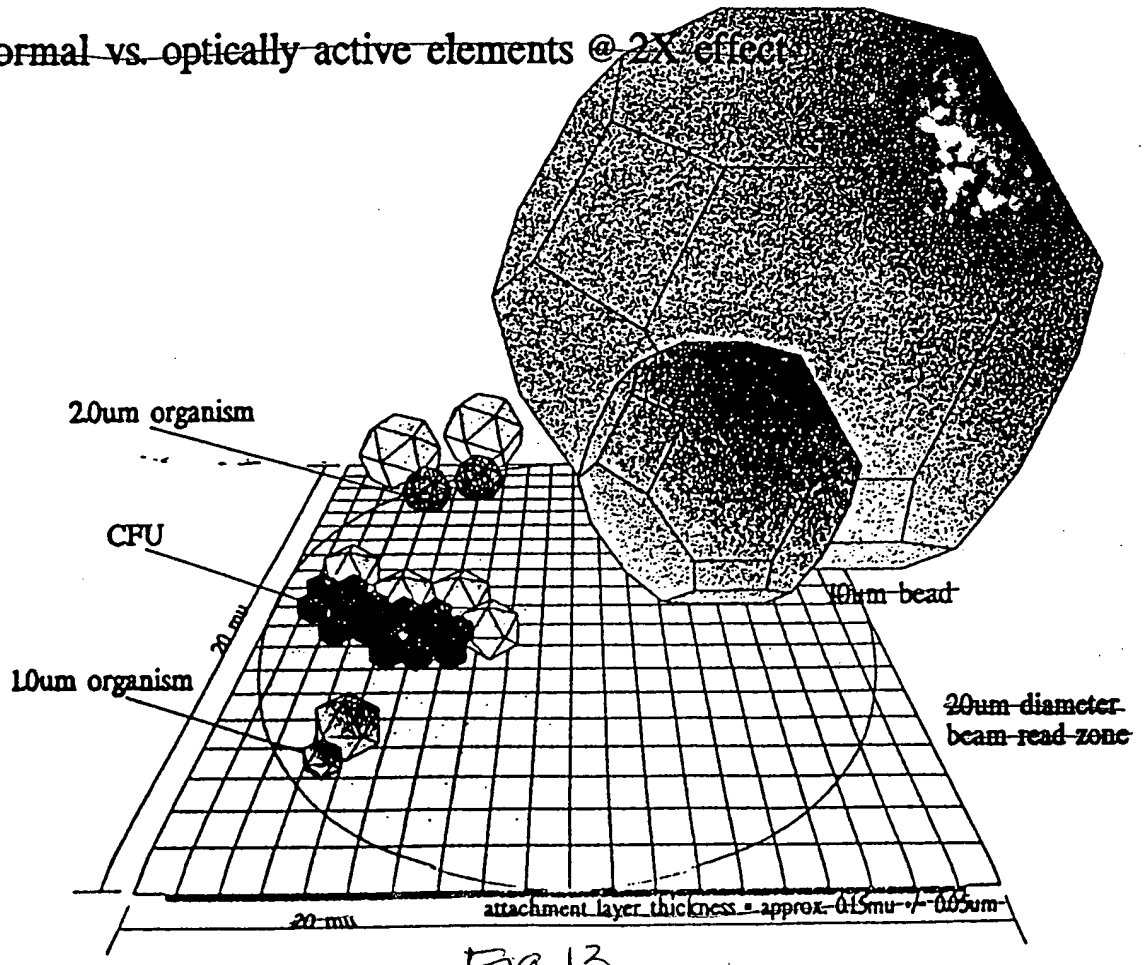

Fig. 13

Figure 14

Annotated Sheet

14/25
~~15/15~~

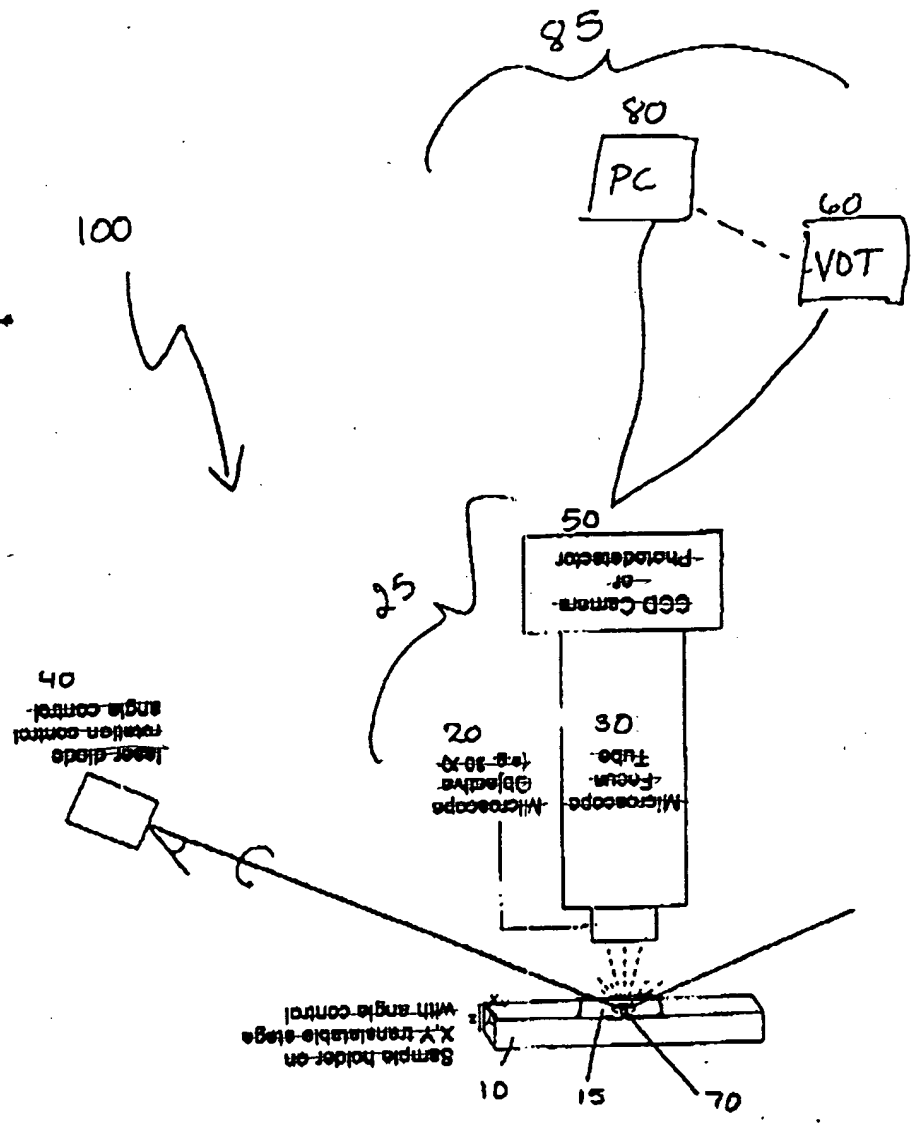

Fig. 5 14

Annotated Sheet

15/25

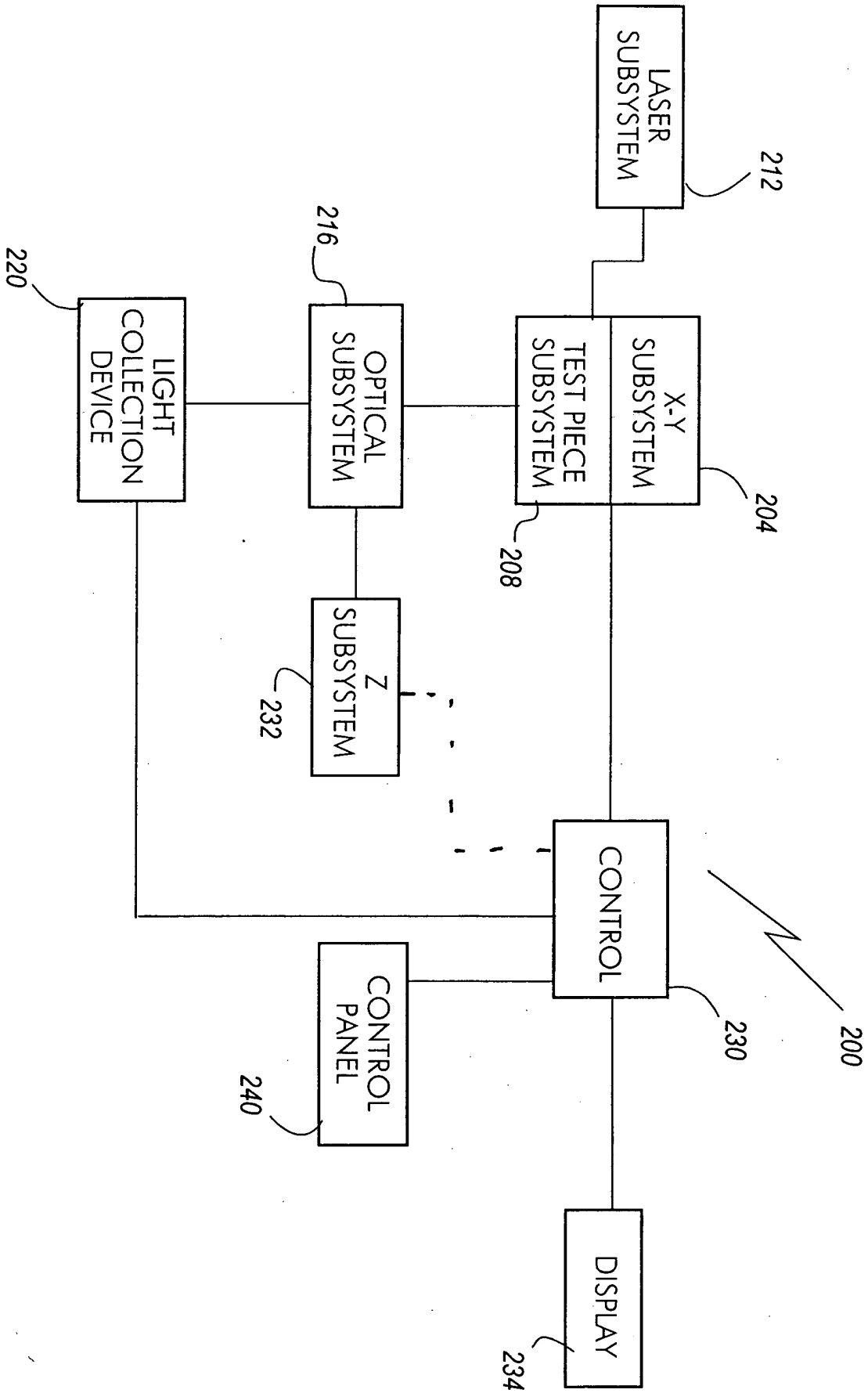

FIG. 15

Annotated Sheet

16/25

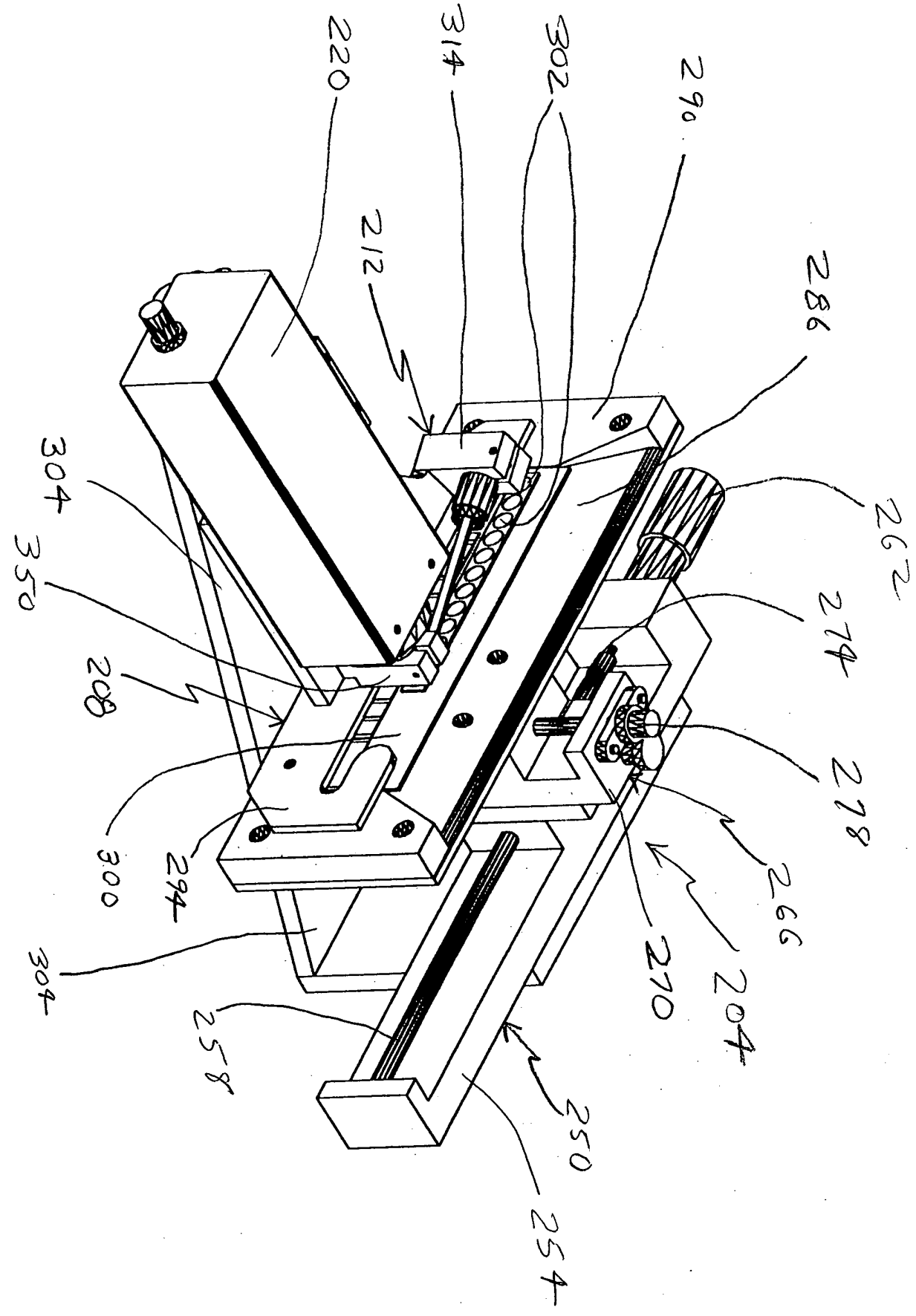

FIG. 16

NOTES: UNLESS OTHERWISE SPECIFIED

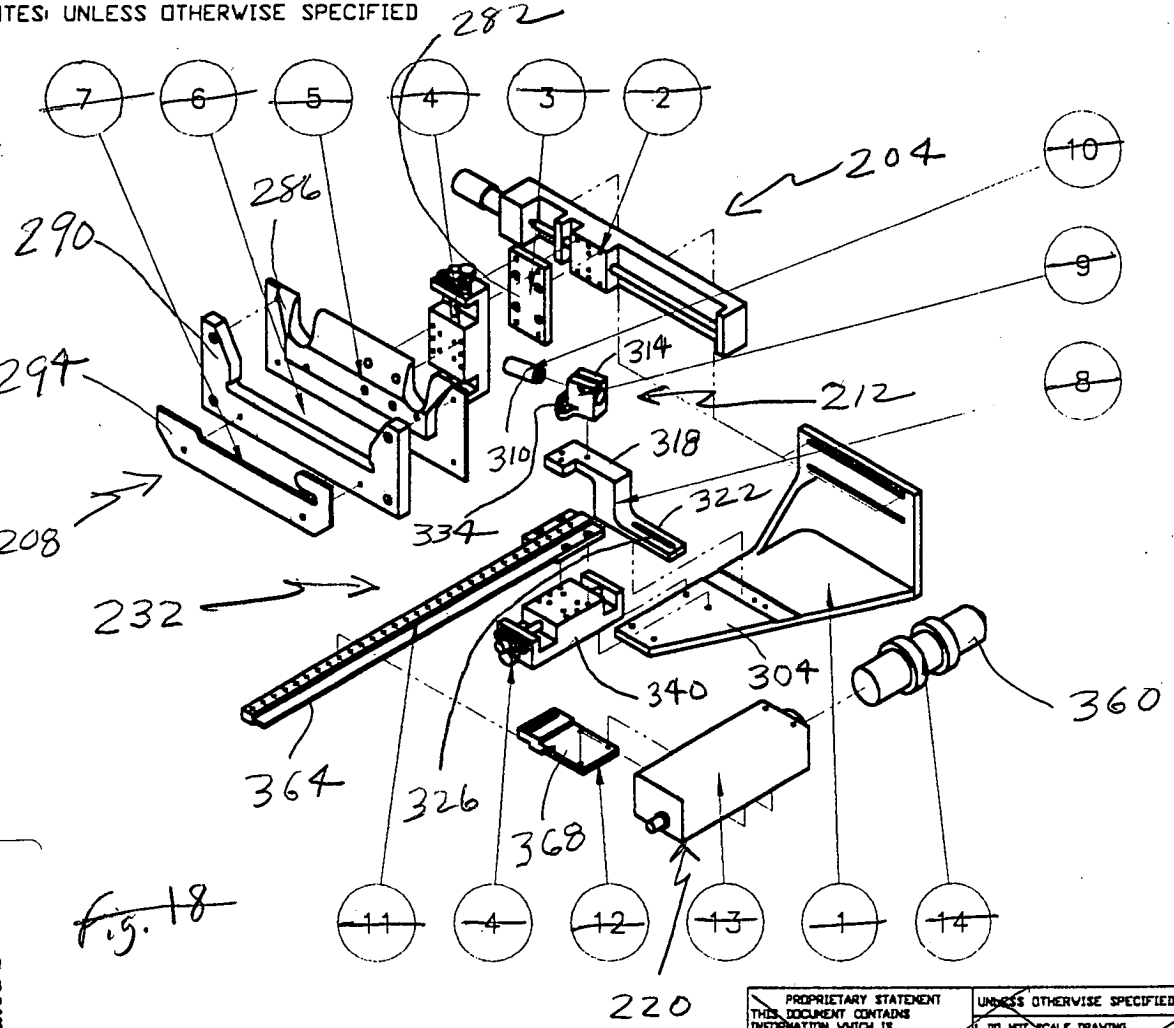

Fig. 17

Fig. 18

Item	Qty	PART
14	1	OBJECTIVE
13	1	CAMERA
12	1	CAMERA PLATE
11	1	Z PLATE
10	1	LASER
9	1	LASER HOLDER
8	1	LASER SUPPORT
7	1	TEST PIECE TOP
6	1	TEST PIECE SIDE
5	1	TEST PIECE BASE
4	2	MM-4M-F-25
3	1	X-Y PLATE
2	1	MM-4M-EX-108
1	1	BASE PLATE

Parts List

REVISIONS

ZONE	REV	DESCRIPTION	DATE	APPROVED
-	-	-	-	-

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XX (X.XXX) = ± .13 (.005)
XXX (X.XXXX) = ± .013 (.0005)
X.X° = ± .25

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TITLE: DDX ILLUMINATOR SYSTEM ASSEMBLY DRAWING

SIZE B | TYPE MACH | DWG. NO. | REV. 2
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ZONE	REV.	DESCRIPTION	DATE	APPROVED
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10/25

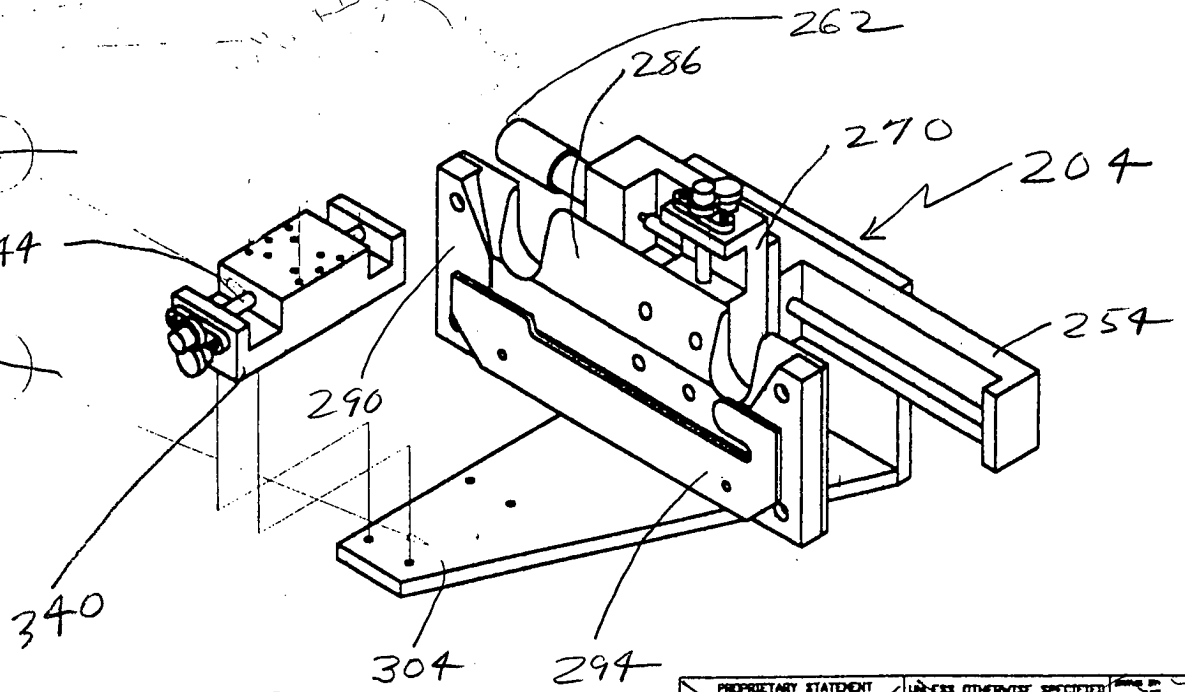

Fig. 19

Fig. 18

Item	Qty	Name
5	5	FORTH ASSEMBLY
4	4	MM-4M-F-25
3	3	Z-PLATE
2	2	LENS CELL HOLDER
1	1	LASER HOLDER

Parts List

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5. TOLERANCES ARE:
.X [X.XX] = ± .5 [.02]
.XX [X.XXX] = ± .13 [.005]
.XXX [X.XXXX] = ± .013 [.0005]
X.X° = ± .25

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Scintilla 4901 W. 93rd Av. Apt 2232 Westminster, CO 80031 (303) 857-2858

TITLE: DDX ILLUMINATOR SYSTEM FORTH MECHANICAL ASSEMBLY

SIZE: B — TYPE: MACH — DWG NO. — REV: 1

SCALE: 1/1 — CONTRACT — SHEET 1 OF 1

Annotated Sheet

OPTICAL BENCH. LIGHT RAYS ARE MODELED IN THIS RENDERING. THE LASER IS SHOWN AT THE NOMINAL 13.5° FROM THE TEST PEICE. IT IS ADJUSTABLE FROM 4.5–34.5°. THE LASER AND LENS CELL HOLDERS ARE C–CLAMPS. THEY WILL BE MACHINED SUCH THAT A SET SCREW IS NTO NEEDED, BUT IN THE FUTURE IT MAY BE NEEDED SO THE SET SCREW WILL BE MACHINED NOW (AS SHOWN). THE LENS CELL HAS ADJUSTABILITY VERTICAL TO THE TEST PEICE WITH STRAIGHT PIN–N–SLOT & ONE RETENTION SCREW IN THE SAME MANNER AS THE LASER HAS ROTATIONAL ADJUSTABILITY.

19/25

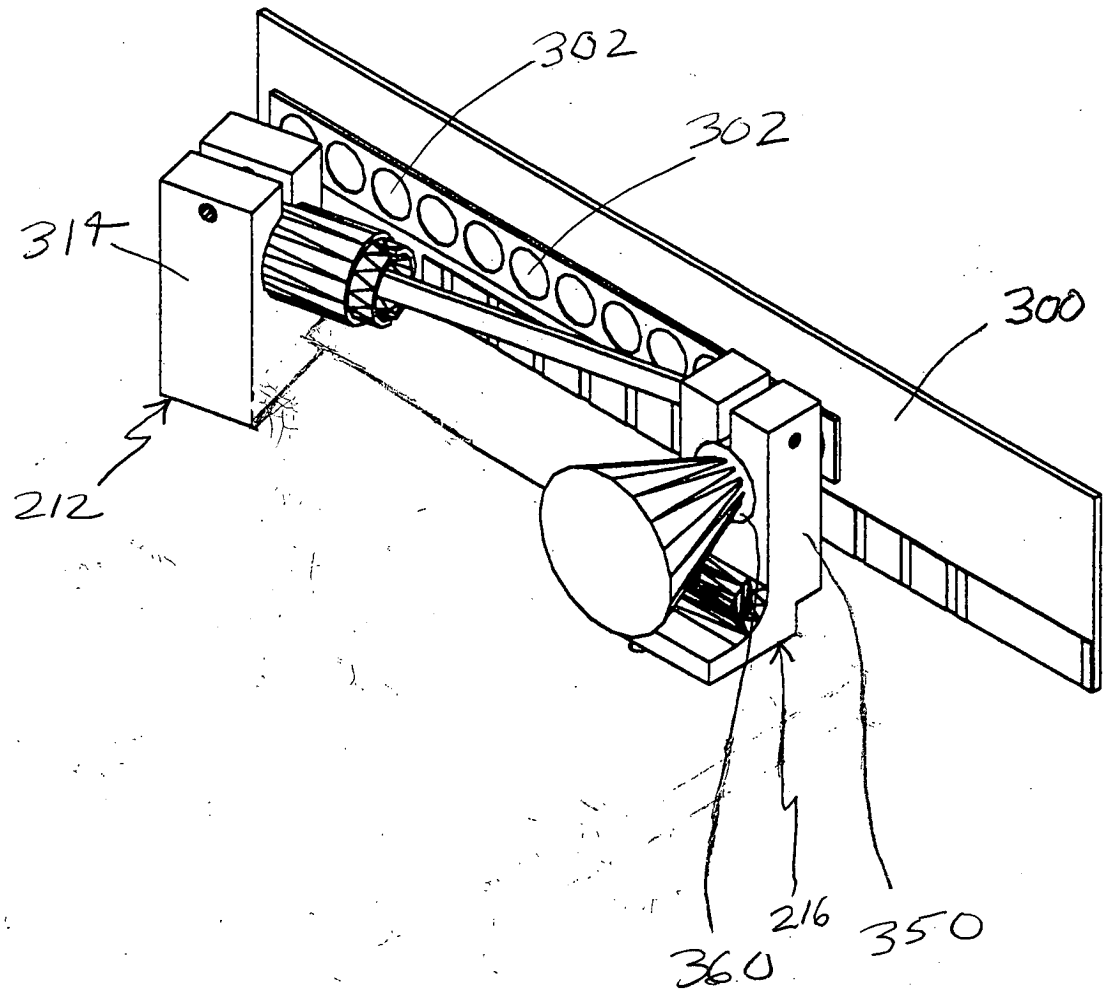

Fig. 20

Fig. 19

Annotated Sheet

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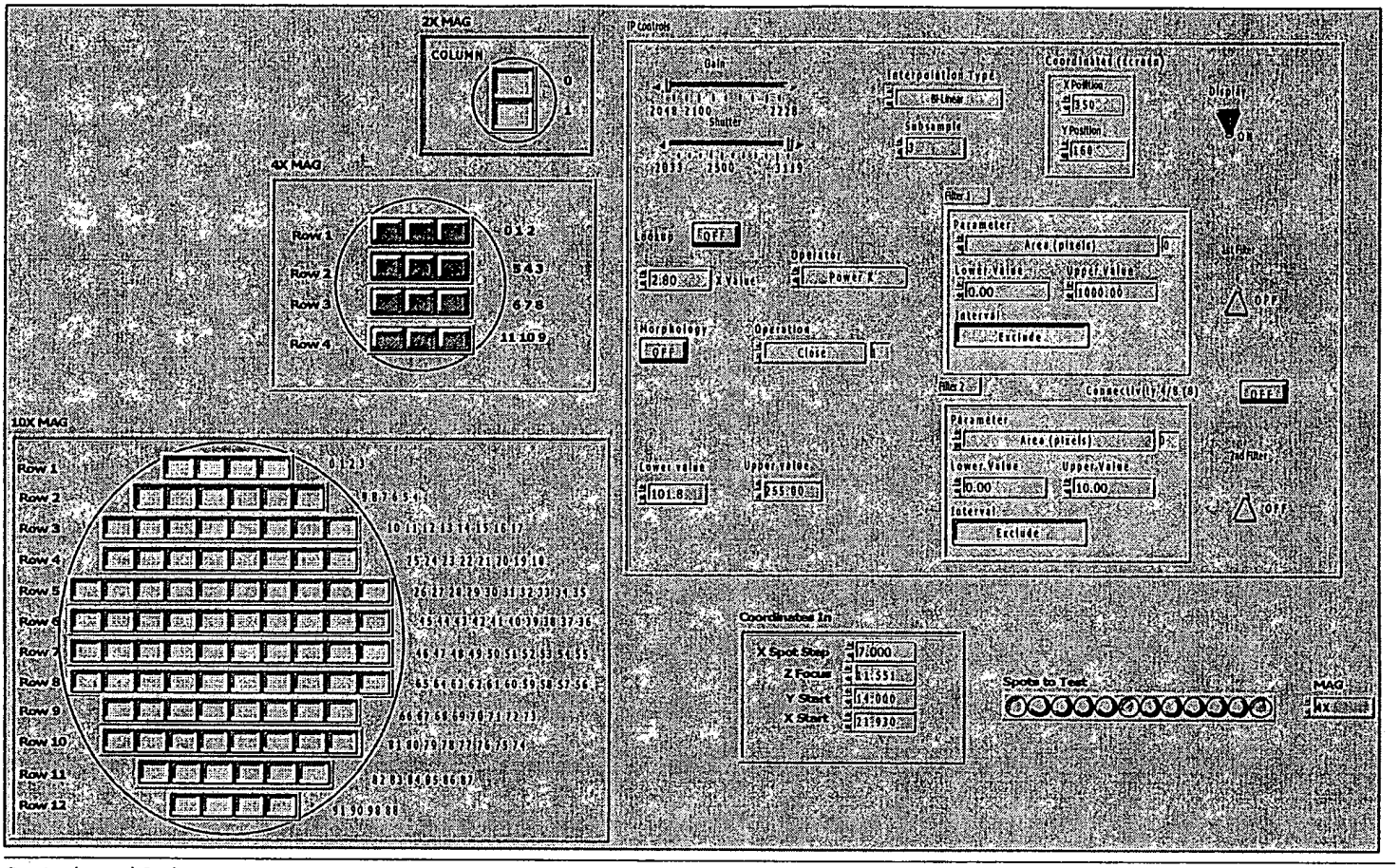

Controls and Indicators

- MAG
  - 2X MAG
    - COLUMN
      - Boolean
  - 4X MAG
    - Row 1
      - Boolean
    - Row 2
      - Boolean
    - Row 3
      - Boolean
    - Row 4
      - Boolean
  - 10X MAG
    - Row 1

Fig. 20

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Printed on 11/15/2001 at 1:08 AM

Front Panel

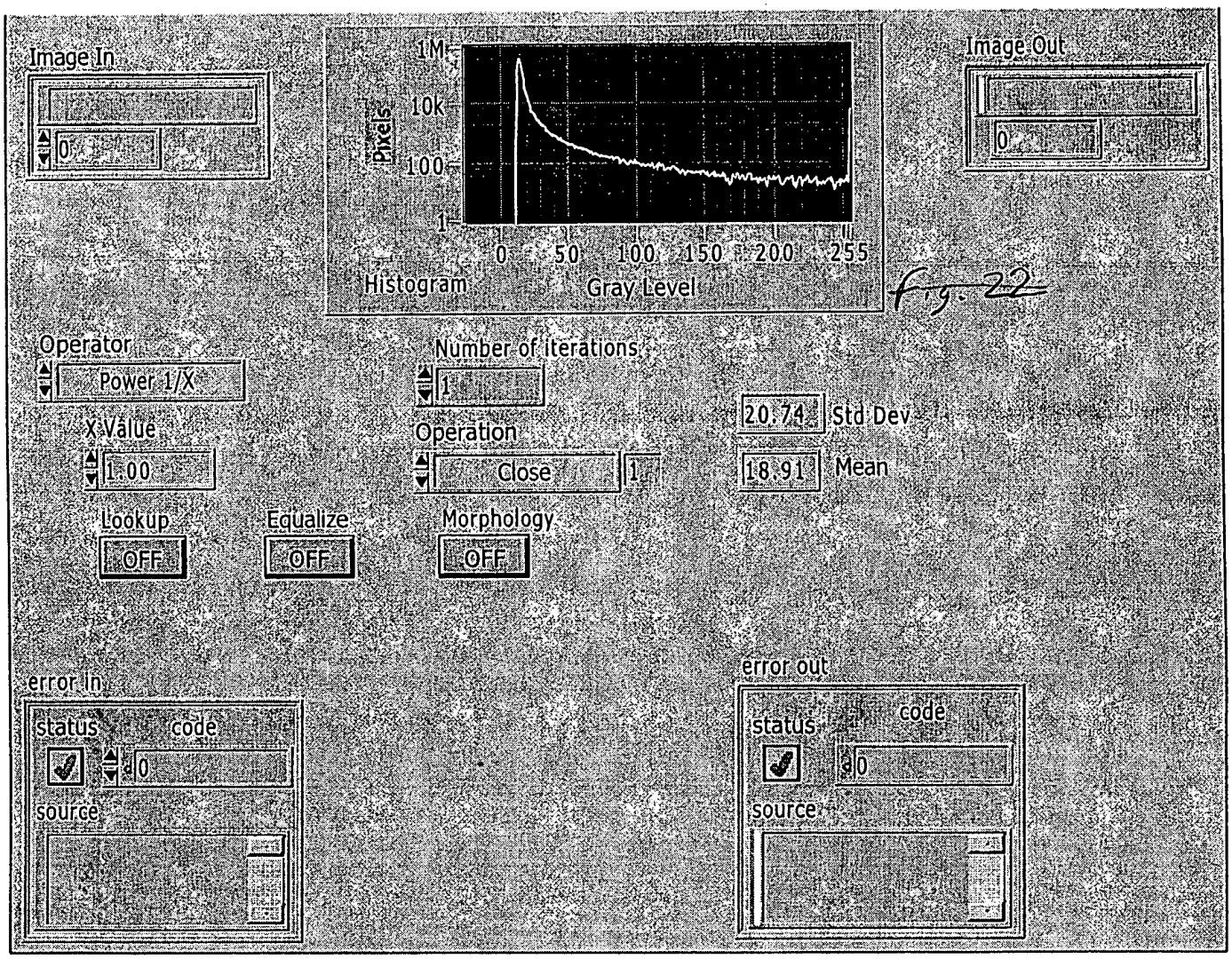

Fig. 22

Controls and Indicators

Fig. 21

Operator
Operator specifies the remapping procedure used.

X Value
X Value is a value used only for the operators Power X and Power 1/X.

Equalize

Operation
Operation specifies the type of morphological transformation procedure to use.

Lookup

error in
The <B>error in</B> cluster can accept error information wired from VIs previously called. Use this information to decide if any functionality should be bypassed in the event of errors from other VIs.

The pop-up option <B>Explain Error</B> (or Explain Warning) gives more information about the error displayed.

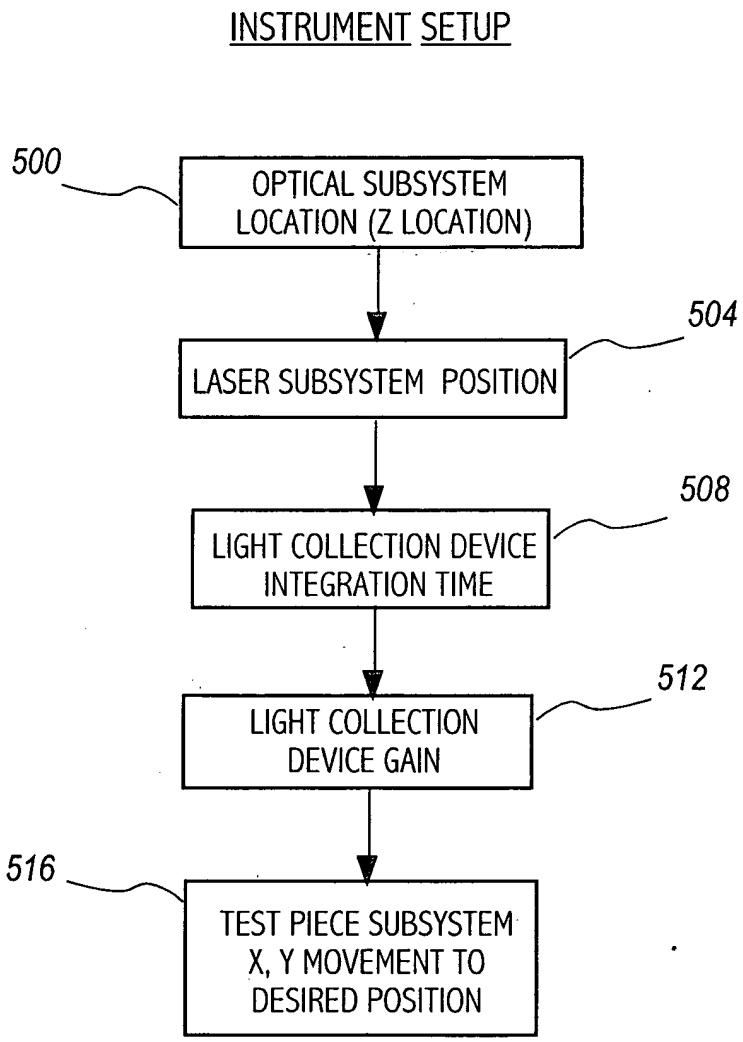
INSTRUMENT SETUP
500
OPTICAL SUBSYSTEM LOCATION (Z LOCATION)
504
LASER SUBSYSTEM POSITION
508
LIGHT COLLECTION DEVICE INTEGRATION TIME
512
LIGHT COLLECTION DEVICE GAIN
516
TEST PIECE SUBSYSTEM X, Y MOVEMENT TO DESIRED POSITION

Fig. 22

FIG. 22

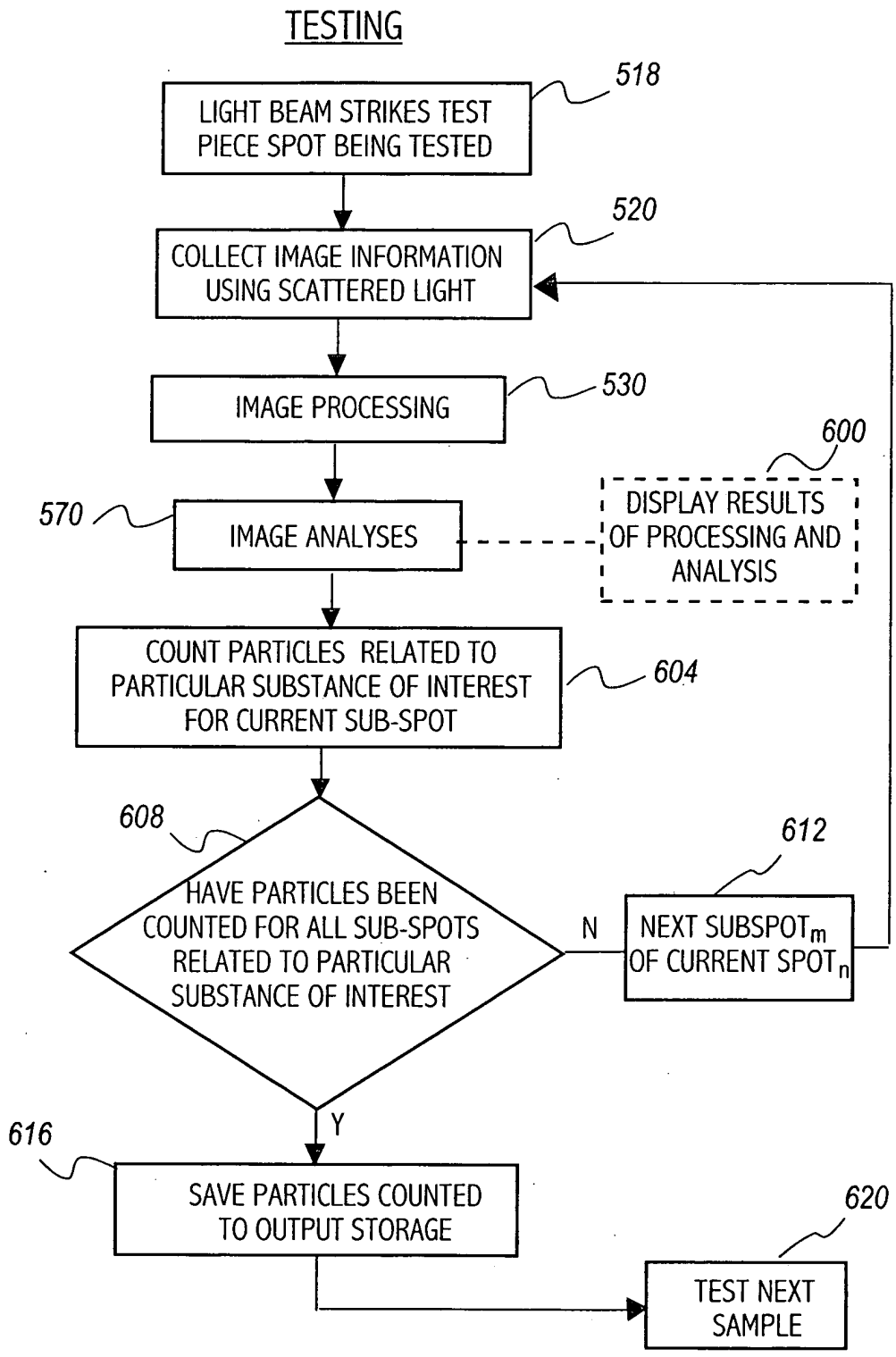
TESTING
LIGHT BEAM STRIKES TEST PIECE SPOT BEING TESTED
518
COLLECT IMAGE INFORMATION USING SCATTERED LIGHT
520
IMAGE PROCESSING
530
600
570
IMAGE ANALYSES
DISPLAY RESULTS OF PROCESSING AND ANALYSIS
COUNT PARTICLES RELATED TO PARTICULAR SUBSTANCE OF INTEREST FOR CURRENT SUB-SPOT
604
608
HAVE PARTICLES BEEN COUNTED FOR ALL SUB-SPOTS RELATED TO PARTICULAR SUBSTANCE OF INTEREST
612
N
NEXT SUBSPOT$_m$ OF CURRENT SPOT$_n$
Y
616
SAVE PARTICLES COUNTED TO OUTPUT STORAGE
620
TEST NEXT SAMPLE

FIG. 23

FIG. 23

IMAGE PROCESSING

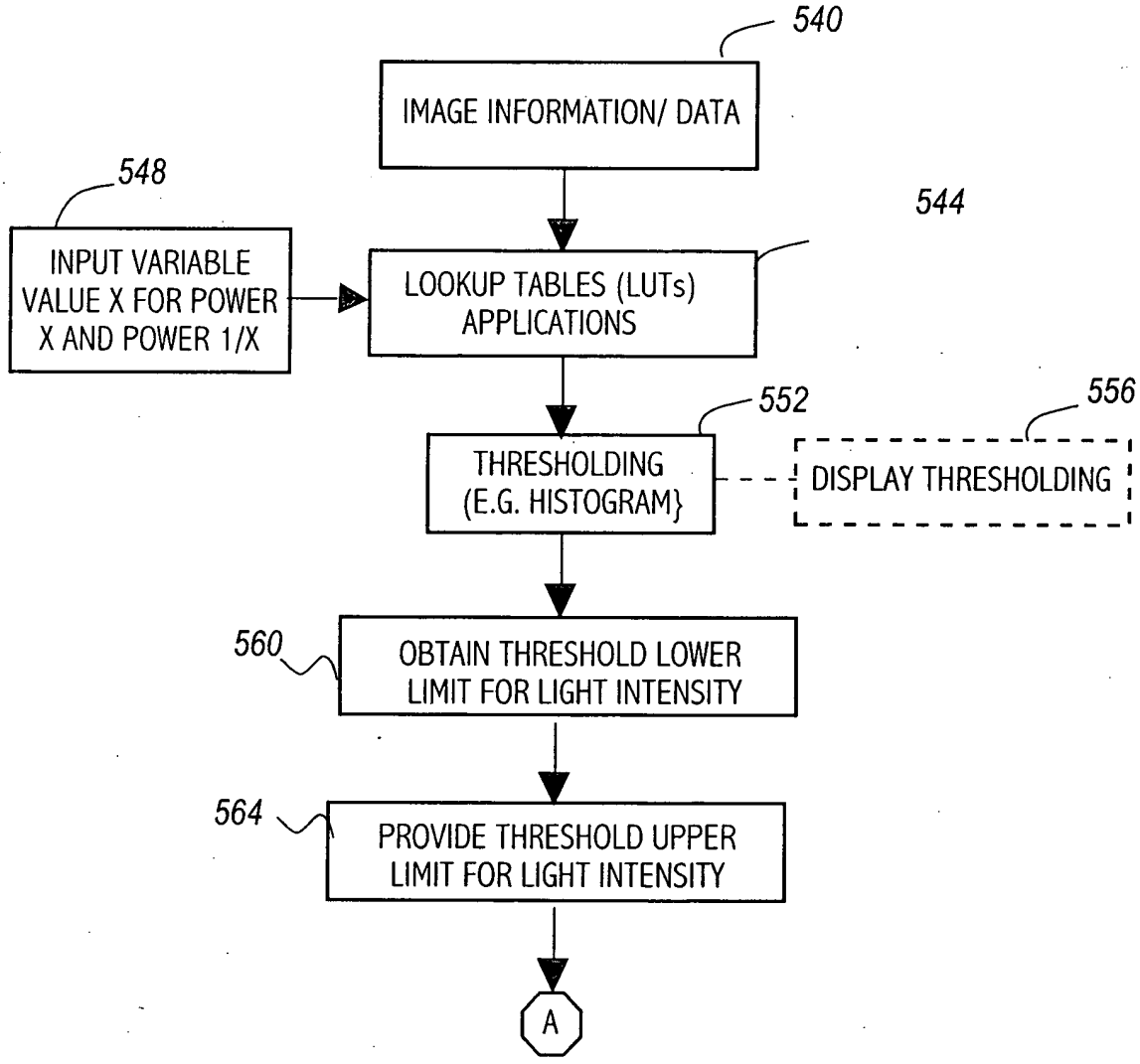

Fig. 24

FIG. 24

IMAGE ANALYSIS

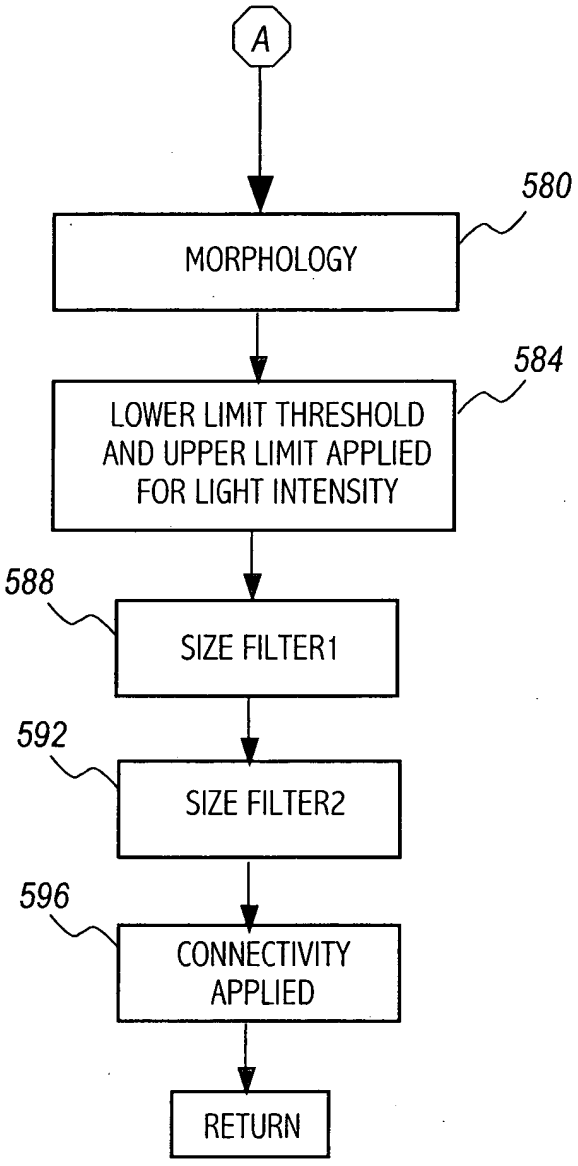

Fig. 25

FIG. 25